Deleterious combined effects of salt-loading and endothelial cell restricted endothelin-1 overexpression on blood pressure and vascular function in mice.

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Abstract

BACKGROUND:

We previously showed that young transgenic mice overexpressing preproendothelin-1 specifically in endothelial cells had hypertrophic remodeling, endothelial dysfunction, increased vascular NADPH oxidase activity, and inflammation in mesenteric small arteries without blood pressure (BP) elevation compared to nontransgenic wild-type littermates. To assess the consequences of salt-loading and the role of endothelin receptors, we investigated the effects of these on vascular structure, function, and oxidative stress in mesenteric arteries in salt-loaded transgenic mice treated with endothelin receptor antagonists.

METHODS:

Ten-month-old male transgenic and wild-type littermates were salt-loaded (4% NaCl) and treated with endothelin subtype A receptor antagonist (ET(A)RA, ABT-627, 5 mg/kg per day), endothelin subtype B receptor antagonist (ET(B)RA; A-192621, 30 mg/kg per day), or ET(A)/BRA (bosentan, 100 mg/kg per day) for 4 weeks. BP was measured by radiotelemetry, vascular reactivity of mesenteric small arteries was studied on a pressurized myograph, and vascular NADPH oxidase activity was studied by lucigenin chemiluminescence.

RESULTS:

Transgenic+salt mice had significantly increased BP compared with wild-type+salt mice, which was prevented by ET(A)RA and dual ET(A/B)RA but further increased by ETB antagonism. Increased small artery media/lumen ratio of transgenic+salt mice was significantly decreased only by dual ET(A/B)RA ($P < 0.01$), whereas no differences were found in media cross-sectional area. Impaired maximal relaxation of small arteries to acetylcholine was significantly prevented with ET(A)RA and ET(A/B)RA ($P < 0.05$). N(omega)-nitro-L-arginine methyl ester-induced reduction of acetylcholine maximal relaxation was partially prevented by ET(A)RA, completely prevented by dual, and partially restored by vitamin C preincubation following dual ET(A/B)RA. The blunted endothelin-1 contractile response of small arteries found in transgenic+salt mice was partially restored by ET(A)RA and completely prevented by dual ET(A/B)R antagonism. The vasoconstrictor response to endothelin-1 was not altered in the presence or absence of ET(B)RA. Increased vascular NADPH oxidase activity of transgenic+salt mice was further increased by ET(B)RA but returned to levels seen in wild-type+salt mice under either ET(A)RA and ET(A/B)RA.

CONCLUSION:

Transgenic+salt mice with endothelin-1 overexpression have structural alterations of mesenteric resistance vessels, endothelial dysfunction due to reduced nitric oxide bioavailability, a reduced responsiveness to endothelin-1, and enhanced vascular NADPH oxidase activity. ET(B)RA further exacerbated these effects, whereas ET(A)RA significantly improved but did not normalize them in chronically salt-loaded transgenic mice with endothelial cell human endothelin-1 overexpression. Salt and endothelin-1 overexpression have deleterious additive effects on vascular remodeling mediated by ET(A)R and ET(B)R. ET(B)R probably located in the endothelium, however, also exerts beneficial effects on endothelial function in this experimental paradigm. The present study provides the first in-vivo demonstration that endothelin-1 overexpression when associated with high-salt intake results in enhanced endothelial dysfunction and vascular remodeling of resistance vessels, and contributes to elevated BP, via ET(A)R and ET(B)R.